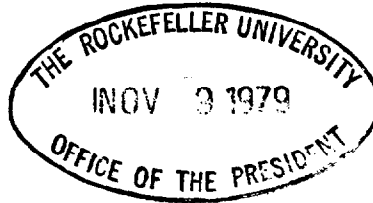


Joshua Lederberg
The Rockefeller University
York Avenue and 66th St.
New York, New York



November 4, 1979

Dear Dr. Lederberg:

Fellowship proposals are, once again, becoming an important part of my life, and I must ask once more for recommendations. ✓

Since we last had a chance to talk, I explored some of the possibilities for training in human genetics that we discussed at that time, but none of the people that I got in touch with could offer me the kind of training opportunities that I wanted. My fellowship in aging finally did get funded (only a year and a half after my application), but since Pauline Yahr had altogether lost interest in aging research by that time, I am now working in Gary Lynch's lab. So far, I've been spending quite a lot of time following up on some earlier work done in the lab on corticosterone and aging, but we've just gotten some new equipment for doing neurotransmitter assays that should simplify my proposed research.

Another consequence of my work with Dr. Lynch has been a new idea about the hormonal mediation of behavior that occurred to me in the middle of a conversation about changes in synapse number following long-term potentiation in the hippocampus. I'm wondering if the ability of hormones to induce protein synthesis might lead to changes in synapse number within brain regions, and if that might be a mediating mechanism in hormone-dependent behaviors. The work that's being done here and in other labs on brain plasticity got me wondering about this, and I can't find anything in the literature that definitely rules it out.

In fact, a number of things have turned up in my reading that make the idea seem even more attractive. The most striking data are Toran-Allerand's findings that estrogen and testosterone stimulate axonal growth in cell cultures of neonatal preoptic area and hypothalamus. Taken together with the report by Gorski and company that the volume of the sexually dimorphic nucleus of the preoptic area is larger in animals exposed neonatally to gonadal hormones, this at least suggests that masculine sexual behavior in adults might be influenced by the number of connections in the area. No one else seems to have been struck by the idea that testosterone might be capable of stimulating the formation of new connections in adult brains, so I've written a fellowship proposal to try to persuade the NSF to underwrite my learning enough about electron microscopy to look at the possibility.

The idea does provide a framework that fits some of the existing data more comfortably than the idea that hormones act largely by affecting neurotransmitter release. This is particularly true for the pattern of masculine sexual behavior after castration. The behavior declines rather gradually in experienced males, and some parts of the pattern are still displayed weeks after testosterone levels have dropped to zero. Also, once the behavior has disappeared, it takes a period of time to bring it back with testosterone therapy. Also, it requires a lower dose of testosterone to maintain sexual behavior, starting immediately after castration, than it does to reinstate it after it disappears. I think that the idea that this may be a function of the loss and regrowth of synaptic connections makes some sense.

Also, one of the other post-docs in the lab, Kevin Lee, tells me that some adrenalectomized animals he's been looking at in connection with a study of corticosterone effects on learning seem to have fewer synapses in the hippocampus than the controls do. This came as a surprise to Kevin, but I thought it was fascinating. He hasn't done enough animals yet to be absolutely sure that this is what's happening, and it's definitely not for general circulation, but it certainly looks interesting viewed from my perspective.

The strongest data on the other side come from a study by Reier in which no sex difference appeared in a sample of preoptic area in neonatal animals, but I don't put much faith in it for several reasons. First, he seems to have looked all over the preoptic area, and I think that the sexually dimorphic nucleus is a better place to focus. Second, he only reports total synapse numbers. Since Raisman and Field found sex differences only in a subpopulation of synapses in the dorsal preoptic, and since the work here on the anatomy of long-term potentiation effects also suggests that the changes are limited to one type of synapse, I think that his analysis may have glossed over any effects. Finally, I'm not very impressed by the quality of the micrographs that he's published. I think that I can do better.

I'm not very happy about spending more time learning a new technique, and continuing to be a post-doc for another year, but I don't see any other way to test the idea, and the idea is very attractive.

I'm enclosing the proposal, so that you can see the whole background and what I plan to do. I'm sorry that it comes to you on such short notice, but NSF didn't manage to respond to my application with the appropriate forms until late in October. It was a good thing that I'd already written down some of my ideas, so that I didn't have to do the whole thing from scratch in a week.

Otherwise, I'm busy on a variety of projects. I'm working on a paper on the maternal pheromone studies that I did with Pauline, and that will go to Physiology and Behavior. It's a big paper (she doesn't believe in sending out work that amounts to a progress report, and I can understand that, but it hasn't done my vita any good), and it shouldn't face any problems in getting published. We have two novel findings: a new mechanism of pheromone production and data that indicate that pups can recognize individual male odors. We also had a paper out in Hormones and Behavior last year that I'm enclosing too. Gary and I collaborated on the paper for the aging conference at Wood's Hole, which you may have seen, and that should come out sometime in the next year. I was sorry that you didn't make it to the conference; I was looking forward to seeing you again. The conference was interesting, even though it didn't lead immediately to any new research ideas.

Please let me know what you think of the proposal. I'm really excited by the idea, and I hope that the reviewers like it.

Sincerely,

A handwritten signature in cursive script, appearing to read "Paula", written in dark ink.